these cases, while bearing in mind the possibility of their being distinct infectious diseases of the nervous system, which may escape detection because of a general similarity in their clinical manifestations to well-recognized entities does not aid in establishing lethargic encephalitis as a definite clinical entity.

THE SIGNIFICANCE OF CERTAIN PULMONARY LESIONS IN RELATION TO THE ETIOLOGY OF INFLUENZA.

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The great variations in the results of bacteriological analyses of the lungs and respiratory tract of those dead of influenza have left no common ground for agreement upon any one microörganism as the etiological agent of this disease. Although in certain sections of the country evidence seemed to be strongly in favor of Pfeiffer's bacillus,[1] the failure to find this microörganism and the predominance of other invading bacteria in different localities have served in large measure to counteract what early seemed to be a confirmation of Pfeiffer's view of the importance of this bacillus in etiological relation to influenza. Nor have the carefully planned and skilfully executed experiments upon human beings in this country, designed to transmit the disease under controlled conditions, lessened our ignorance of a specific causative agent or its mode of transmission, though these experiments were carried out on a large scale and under what appeared to be perfectly adequate conditions.[2] There remains the pathological anatomy of the disease as a possible and perhaps lone source at the present time of some positive knowledge concerning its doubtful cause.

In the absence of bacteriological evidence for a specific etiological agent, the pathologist is confronted with the question whether there are lesions which are typical of the disease, so that one perceiving them may be assured they are the result of influenza *per se*. If this can be satisfactorily established then we have a criterion upon which to evalue the importance and relationship of demonstrable associated infectious agents and may arrive at a tentative conclusion regarding the etiology of the disease. In the absence of such a criterion we shall probably remain, despite the overwhelming losses of the recent pandemic and our abundant opportunity for investigation, in a lack of knowledge respecting it equal to that following the last pandemic of 1889.

[1] Keegan, J. J.: Jour. Am. Med. Assn., lxxi, 1051.
[2] Public Health Reports, January 10, 1919, xxxiii, 34.

The prevailing opinion is, as Wolbach[3] has stated, that death from influenza means death from lung complication—pneumonia in some form—and it is in the lungs that possible characteristic lesions may be found. In 1889 Leichtenstern[4] expressed his conviction from clinical and anatomical evidences that there existed a primary pneumonia produced by the poison of influenza, and from a study of the material which I have had available from the height of the epidemic last fall and subsequently I am convinced that this is true and that the etiological factor is not any one of the numerous pathogenic microörganisms which have been cultivated from the lungs, often in pure culture, but an unknown virus which produces the general intoxication and may produce characteristic lesions in the lungs with or without the coincidence of other infectious agents.

That influenza is due to an unknown agent is a view held by a considerable number of those who have studied the disease from various points of view, but I do not find the impression of specific lesions in the lung prevalent, partially no doubt because most of our reports of the pathology of the recent epidemic have consisted of gross descriptions; and while the evidence for this opinion is not altogether above criticism, I feel that it is strong and well worthy of great emphasis.

The pulmonary lesion to which I would especially refer is a dilated condition of alveolar ducts, with a hyaline membrane partially or completely covering their walls and sometimes those of subtended alveoli. This lesion has been described already by MacCallum,[5] Wolbach[6] and by Burnett and the writer.[7] The membrane is not present within all dilated air spaces and is not uniformly distributed throughout the lung. It may be most conspicuous in areas of the lung which contain least exudate. It is present most conspicuously in acute pneumonia of short duration accompanying influenza. The membrane is irregular in thickness, sometimes stratified, with occasional cells within narrow clefts. It is usually thickest over the angles of the wall, but may completely fill an alveolus. At its margins it may be continuous with strands of fibrin, though it does not give the staining reactions for fibrin. In some preparations it appears to be composed almost entirely of fused necrotic mononuclear cells, in others of coalescing strands of fibrin, and probably always represents a mixture of the two. Associated with this lesion are evidences of injury and acute reaction, such as hemorrhage, edema, cellular and fluid exudate and focal necrosis of alveolar walls, each of which varies in extent in

[3] Johns Hopkins Hospital Bulletin, vol. xxx, 338, 104.
[4] Specielle Path. u. Ther., Nothnagel, iv, No. 1, p. 83.
[5] Jour. Am. Med. Assn., lxxii, 10, 720.
[6] Loc. cit.
[7] Goodpasture, E. W., and Burnett, T. L.: U. S. Naval Medical Bulletin, xiii, 2, 177.

different cases. The hyaline membrane is always associated with dilated alveolar ducts. This lesion is not to be considered specific in the sense that it contains specific elements in its composition, for so far as has been demonstrated it represents a reaction to injury by elements normally participating in inflammatory processes. The evidence for its specificity depends solely upon the constancy of its association with influenza and its absence in other types of pulmonary inflammation known to be of a different nature. So far as I am aware it has not been described in any inflammation of the lungs other than that accompanying influenza. Wolbach describes it as constantly present in the cases of influenzal pneumonia studied by him, and considers its presence "the one distinctive feature in the pathology of influenzal pneumonias, and its constant occurrence indicative of the entity of the initial lung infection." I found it present in all of the cases of influenzal pneumonia which died within a few days after the onset, and in 70 per cent. of the total number of pneumonias accompanying influenza examined during the height of the epidemic. Failure to find it only occurred in cases of outspoken secondary lobar pneumonia and streptococcus infections with extensive necrosis of the pulmonary tissue. MacCallum describes the same lesion as an accompaniment of certain more acute pneumonias following influenza, which he considers due to pneumococci. He does not record the frequency of its occurrence, but since he recovered in the great majority of his cases, pneumococci in pure culture or predominantly, presumably he found it often.

While this lesion is thus seen to have been demonstrated with great frequency in cases dying with pulmonary lesions accompanying influenza during the height of the epidemic, and though it is probably not present in association with any other disease, its presence is, nevertheless, not dependent upon any one demonstrable microorganism, for in the cases studied by Wolbach at Camp Devens, Ayer, Mass., and at Boston, and in those observed by me at the U. S. Naval Hospital, Chelsea, Mass., it was more commonly associated with Pfeiffer's bacillus, often in pure culture; and in the three groups of cases investigated by MacCallum at Camp Lee, Camp Dix and at the Johns Hopkins Hospital, it was accompanied by infection with pneumococci in pure culture or predominantly. Since my former report[8] I have encountered the same lesion in three individuals dying from clinically typical influenzal pneumonia, from the lungs of whom hemolytic streptococci were grown in pure culture, and from two others in whose lungs no microörganisms could be demonstrated either by cultural methods, animal inoculation or microscopic examination of the tissues.

From this evidence it may safely be stated that the lesion characterized by a hyaline membrane as described, situated upon the

[8] Loc. cit.

walls of dilated alveolar ducts and adjacent alveoli, is not a reaction typical of the presence of any one of the various demonstrated microörganisms with which it may be associated; and it may be present in the lungs of persons dead of influenza, in which no microorganisms are demonstrable by the ordinary methods.

Two explanations for its presence occur to me. First, that it represents an inflammatory reaction which under circumstances of lowered resistance, such as occur with influenza, may be brought about by any pathogenic microörganism or toxic agent that may gain entrance to the lungs. Even if this explanation should prove to be the true one the lesion itself is no less specific, for it is the circumstance of an attending influenza that lays the conditions for its formation. The explanation, however, does not appear to be a good one for the reason that we do not find the membrane present in pulmonary inflammations due to pneumococci, streptococci or influenza bacilli unassociated with epidemic influenza. Furthermore, none of these microörganisms or other demonstrable bacteria are associated in any intimate way with the lesion; in fact, whatever the attending infection, this membrane is usually bacteria-free, and, as will be described later, it may be present without demonstrable associated infection. I have gained the impression that it is formed before the fluid and cellular exudate predominates in the inflammatory process, for it is sometimes found most abundantly at the margin of the more firmly consolidated regions and may be less in evidence where the fluid and cellular elements are most conspicuous.

The second explanation is that it represents an inflammatory reaction to an unknown causative agent of influenza which injures the walls of alveolar ducts at first in a relatively mild degree, causing desquamation and necrosis of epithelial cells and an exudate of large mononuclear cells with some fibrin and serous fluid, all of which become partially concentrated by the inflowing and outflowing respiratory currents of air until they coalesce and adhere to the injured walls. The more extensive injury and reaction, with focal necrosis, hemorrhage and fluid exudate, occur later with the increase in the intoxicating agent and with additional injury brought about by secondary infection of any kind.

Supporting this view it seems to me are the facts that this lesion, so far as we know, occurs only in the inflamed lung of those infected with influenza, the diagnosis of influenza being based upon the pandemic character and extreme infectiousness of a disease of certain clinical manifestations; that it is not exclusively associated with any one microörganism, and the microörganisms with which it may be associated do not produce it in inflammations of the lungs other than those accompanying influenza; that it may be present in typical form in lungs in which no organisms are demonstrable by ordinary methods; and, finally, of those dying of pulmonary

lesions accompanying influenza it is demonstrable in a large proportion of cases.

In emphasizing the importance and apparent specificity of the hyaline membrane upon the walls of dilated alveolar ducts, I do not intend to imply that this is the only lesion produced by the virus of influenza within the lungs; in fact, I would attribute in large part to the action of influenzal virus, *per se*, the extensive injury to the pulmonary tissues with resulting hemorrhage, necrosis and acute exudate in cases dying shortly after pneumonia became manifest, and in the lungs of which few or no microörganisms are demonstrable within the alveolar tissues. Yet it is obviously impossible to determine what degree of this injury might be due to the action of secondary invading microörganisms if they are present, for such injury and inflammation is of a general kind to which any one of the infectious agents might contribute in any degree.

The above-described lesion, then, in man, I believe, may be considered as peculiar to the pulmonary inflammation of influenza, and none of the microörganisms demonstrated in the lungs is essential to its production. These propositions carry the inference that it is a reaction to a specific agent or set of conditions which are present only in this disease. To establish its complete independence of the microörganisms which have been demonstrated in the lungs, we should hope to find it present in certain instances of influenzal pneumonia in which demonstrable microörganisms are not found. At the U. S. Naval Hospital, Chelsea, Mass., we had the opportunity to study two such cases, though I have not found similar instances recorded elsewhere. The prime significance of these observations makes it important that they be described here. The hyaline membrane was present in typical form in each of these lungs, though no microörganisms have been demonstrated in them by culture, animal inoculation or patient study of strained smears and sections by methods which, in other cases with positive cultures, have easily revealed the type of microörganism grown from the lung.

The first instance was that of a large, robust young man who contracted influenza during the height of the epidemic in September, 1918. Clinically, he presented the usual evidences of the disease, and on the fifth day after the onset signs of consolidation in the lungs were first detected. These rapidly spread, intoxication increased and he died on the seventh day after his initial symptoms. Postmortem examination was made two hours after death. Grossly the lungs presented the usual edematous, hemorrhagic, emphysematous condition constantly found in the very acute cases. Cultures were made from both lungs by sterilizing the pleural surface and inserting deeply a capillary pipette withdrawing from various portions a few drops of fluid exudate. This was planted upon whole blood-agar plates, such as had been used successfully in previous cases and which had been properly tested. All of these cultures

proved sterile as well as cultures from the heart's blood. Smears from various portions of exudate, stained with Loeffler's methylene-blue and other routine stains, were likewise negative for micro-organisms. Thin paraffin sections from various regions of the lung were fixed in Zenker's fluid and stained with eosin and methylene-blue, Gram-Weigert and by the anilin-carbol-fuchsin method devised by me to demonstrate Pfeiffer's bacillus in tissues.[9] No organisms were found excepting a few intracellular Gram-positive cocci within the bronchial exudate.

Microscopically the lungs showed an extreme degree of injury and destruction of alveolar walls with hemorrhage, edema, a little fibrin and scant cellular exudate. The alveolar ducts were dilated and on the walls of some of them was found the typical hyaline membrane.

The second case was a more unusual one, being the only instance of its kind observed by us, and I have not seen a similar one described.

The patient was a young man, aged eighteen years, who was admitted to the Naval Hospital with a typical attack of influenza. He was sick three days before admission. His illness continued during the last four days of September and first three days of October, 1918. His temperature was 103° F. on admission and fell the following day to normal. No clinical evidence of pneumonia was discovered during this attack. Three days later he was discharged from the hospital. Afterward he at no time felt well. He went home for a few days on furlough, then returned to his work as a hospital-corps man. His cough persisted; he lost weight and gradually became weaker until he had to report to the sick bay. From there he was sent again to the Naval Hospital, Chelsea. He reëntered this hospital November 6, 1918, with cough, pain in the chest, bloody sputum, anemia and signs of bronchopneumonia in the right lower lobe. His temperature on admission was 100.4° F.; pulse, 120; respiration, 28. He expectorated quantities of bright red blood. The pneumonia speedily became massive and spread to the left lung. The clinical records state he became septic, dyspneic and raised much bloody sputum. Serum from patients convalescing from pneumonia following influenza was administered without relief of symptoms. He died on November 9, three days after admission. White blood count on the day after admission was 17,600. Differential count: polymorphonuclear leukocytes, 58 per cent.; mononuclears, 40 per cent.; eosinophiles, 2 per cent. Urine showed a trace of albumin.

Postmortem examination made two hours after death revealed a pale, anemic, moderately emaciated body. There were 200 c.c. of clear fluid in right pleural cavity. The pleural surfaces were dark purple in color and for the most part smooth, though here and there

[9] MacCallum, W. G.: Jour. Am. Med. Assn., No. 10, lxxii, p. 720.

they were slightly thickened and covered by fine granules of fibrin. The right lung was completely consolidated and very firm. On section the cut surface was brick red in color and hemorrhagic fluid could be expressed and ran out of cut bronchi. Hemorrhage instead of edema was the predominant feature. In the left lower lobe patches of similar hemorrhagic consolidation were present. The lung gave the impression of having been injected with blood through the bronchi so that all the air spaces were filled. On closer inspection dilatation of terminal air channels was evident and the alveolar ducts were outlined by gray lines, and there were minute gray points everywhere as if many alveoli were filled with fibrin. Cultures taken from the various lobes, spleen and heart's blood were sterile; numerous smears showed no organisms. A guinea-pig inoculated intraperitoneally with ground lung died in forty-eight hours, but only a clear sterile peritoneal fluid was found, and its blood culture was sterile.

The spleen of this man was a little smaller than normal and quite pale, yellowish gray. On cut surface yellowish and gray opaque foci up to 2 mm. in size were evident. The kidneys were normal in size, but there were a few small hemorrhages in the cortex and moderate edema. Here and there in the wall of the small intestine were bright red hemorrhages measuring 1 or 2 mm. in diameter. The other organs presented nothing of special interest. The heart and valves appeared normal.

Microscopically sections of the lung show a tremendous amount of blood in the air spaces. Alveoli and terminal bronchioles are filled with erythrocytes. There are innumerable foci composed of polymorphonuclears, fibrin, large mononuclear cells and disintegrating hyaline material scattered through the sections. These foci often indicate small areas of necrosis of the alveolar walls. Here and there alveoli are filled with plugs of fibrin. In certain areas there is a great abundance of hyaline material upon the walls of dilated alveolar ducts and in alveoli. This appears to be formed largely of coalesced necrotic mononuclear cells with small amounts of fibrin. Its appearance and arrangement is in every way typical of that found in the lungs of more acute cases of pneumonia accompanying influenza. The inflammatory process in the lungs appears to be subacute, with a terminal exacerbation. In certain alveoli the exudate has undergone organization, and some bronchioles are filled with plugs of organizing exudate. Both larger and smaller bronchi appear normal. The epithelial coat is intact and no exudate excepting erythrocytes and some coagulated albumin, is present. Patient search has revealed no microörganisms whatsoever in this lung.

The spleen on section shows numerous foci of necrosis occupying especially the areas of former Malpighian bodies. Necrotic cells,

polymorphonuclears, strands and networks of fibrin compose these areas, situated about the small arteries.

The kidneys show a glomerular nephropathy with a fibrinous exudate in Bowman's capsule and cellular proliferation of glomerular tufts; some urinary tubules are filled with erythrocytes. Sections through the hemorrhagic points in the intestine show focal lesions in the wall of arterioles, with fibrinous exudate and a few polymorphonuclears. No microörganisms have been demonstrated in any of these lesions after repeated attempts.

While the presence of lesions in the kidney and spleen may be regarded as evidence that this case does not represent a pure influenzal infection, still the pathology of the lungs and the absence of demonstrable infectious agents to account for the acute pulmonary lesions seem to overbalance them in favor of influenza as at least the primary and predominant infection. And it does not seem inconceivable, although rare, that the virus of influenza might persist within the body for six weeks with the production of lesions of the character found in this man.

The clinical histories of these two cases leave little doubt that they are primarily instances of influenzal infection. Both contracted the disease during the height of the epidemic, and manifested typical clinical courses. The first died of his initial infection; the second, though combating successfully for a time his original attack, never quite recovered, and died of the disease a month later. Both presented lesions in the lung which are to be regarded as peculiar to the pulmonary inflammation of influenza, yet no microörganisms were demonstrated by the usual methods in the lungs of either. In the absence of any known infectious agent one is led to the conclusion that they represent instances of fatal influenzal pneumonia, caused by an infectious agent of which we are totally ignorant, and without secondary invasion of the lungs by any of the pathogenic bacteria commonly found associated with it. Granting that they are examples of influenzal pneumonia, the presence of the hyaline membrane on the walls of dilated alveolar ducts is further evidence of the specificity of this lesion and its independence of secondary invading organisms; or from analogy to other cases the presence of this membrane indicates that the pulmonary inflammation is that of influenza, though no bacteria are found. The pathology of the lungs in the second case is strongly suggestive of a persistence of the infecting agent in this tissue from the time of the initial attack one month previously, with a final and fatal exacerbation.

In interpreting these observations one feels justified in formulating the opinion that influenza is a distinct disease, recognizable clinically only by its epidemic proportions and extreme infectiousness, characterized pathologically by peculiar lesions in the lung, and caused by an unknown virus which gains entrance through the respiratory tract.